

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE****IN RE US APPLICATION OF JONES ET AL****DEC 22 2004****TECH CENTER 1600/2868**

SERIAL NO. 09/810,458

GROUP ART UNIT: 1623

FILED: March 16, 2001

EXAMINER: Paul Zucker

TITLE: PROCESS FOR PREPARING 3-ISOCHROMANONE

DECLARATION PURSUANT TO**37 CFR 1.132**

I, ALAN JOHN WHITTON, a British subject residing at 2 Hillcrest Road, Falkirk, Stirlingshire, FK1 5NH, United Kingdom, declare that:

1. I am the Alan John Whitton named as an applicant in US Application Serial No. 09/810,458 filed March 16, 2001 (the subject application) and that I am familiar with the content of that application.
2. I am a qualified and experienced chemist holding the degrees Bachelor of Science and Masters of Science from the University of Waikato, New Zealand and Doctor of Philosophy from the University of Cambridge, England. I am a Member of the Royal Society of Chemistry and hold the status of Chartered Chemist. I have been employed for 15 years in the Technology and Projects Department of SYNGENTA Limited (formerly Process Technology Department of Zeneca Limited and before that, Imperial Chemical Industries PLC) at its Agrochemicals manufacturing site at Earls Road, Grangemouth, Stirlingshire, FK3 8XG, United Kingdom, having joined the company in 1990 as a Research and Development chemist. During my career with SYNGENTA I have largely worked on the chemistry of agrochemical products, mainly devising and developing processes to agrochemical products and intermediates for their production on an industrial scale. I currently hold the position of Chemistry Work Group Leader in the SYNGENTA Technology and Projects Department.
3. I am the author or co-author of at least 8 publications and a named inventor on at least 9 patents and patent applications.

4. A number of experiments have been carried out using a range of hindered amine bases and tertiary alcohol solvents. All experiments were carried out using the process described in detail below, the only difference being that a different base or different solvent was used. The hindered amine bases used were Hünig's base (N,N-diisopropylethylamine), triethylamine, tri-n-butylamine, tri-isobutylamine, tri-n-hexylamine and N,N-dimethylcyclohexylamine. No comparison was made with trimethylamine, which is a gaseous product at room temperature. The solvents used were tertiary amyl alcohol, pinacol (2,3-dimethyl-2,3-butanediol) and 3,7-dimethyl-3-octanol.

5. The results show that by far the best yield was obtained using Hünig's base when compared with other hindered amine bases, including the triethylamine and tri-n-butylamine referred to in US 5,886,211 (Hirai *et al*), in the same tertiary amyl alcohol solvent. They also show that good yields were obtained using alternative tertiary alcohol solvents.

6. Process Methodology

o-Xylene- α,α' -dichloride (OXDC), palladium catalyst, triphenylphosphine, Hünig's base, water and tertiary amyl alcohol, in that order, are charged to a pressure vessel (autoclave) using tertiary amyl alcohol solvent to wash in any residual solids. The autoclave is then sealed and purged with carbon monoxide at 3 x 5 barg pressure before finally pressurizing to ~ 4 barg. The reaction mixture is agitated at ~1000 rpm and heated to 70°C. It is then held under these conditions for 3 to 4 hours. As necessary, further carbon monoxide is charged to maintain the pressure. At the end of the reaction, the pressure is released to ~1 barg.

An aqueous solution of caustic soda is charged to a separate jacketed reaction vessel (JRV) and brought to 60°C. The contents of the autoclave are also brought to 60°C and discharged to the JRV. The JRV liquors are stirred for 1 hour at 60°C and allowed to stand for 30 minutes to ensure phase separation. The lower basified aqueous phase (containing ring-opened 3-isochromanone) is separated from the upper organic phase. The basified aqueous phase is reintroduced to the JRV followed by o-xylene. Hydrochloric acid (at 60°C) is then cautiously added to effect ring closure of the 3-isochromanone and to extract it into the o-xylene phase. After stirring for 1 hour at 60°C, separation of the phases gives an acidic aqueous waste stream and a o-xylene solution of 3-isochromanone.

7. Materials

Material	Act.Wt. / g	Str. / %	100% Wt. / g	MW	Moles / mmol	Ratio
OXDC	14.7	95	14.0	175.06	80	1.00
Hünig's Base	31.4	99	31.0	129.25	240	3.00
Triphenylphosphine	0.465	99	0.46	262.29	0.00175	0.022
t-Amyl alcohol	21.12	100	21.12	88.0	240	3.00
Water	28.8	100	28.8	18.00	1600	20.00
PdCl ₂ sol n. on Pd assay *	0.079	21.62	0.017	106.42	0.16	0.002
Triphenylphosphine	0.465	99	0.46	262.29	0.00175	0.022
Caustic soda (aq)	48.76	21	10.24	40.0	256.0	3.20
Xylene	42.5	100	42.5	106.17	400	5.00
HCl	12.98	36	4.67	36.5	128	1.60

*ex Johnson Matthey Bx DH0480. The palladium catalyst is blended with half the triphenylphosphine charge prior to addition.

8. This procedure was repeated substituting other tertiary amine bases for the Hünig's base. The amount of base used was the same in molar terms as the amount of Hünig's base used. The procedure was also repeated substituting alternative solvents for the tertiary amyl alcohol. Again, the amount of solvent used was the same in molar terms as the amount of tertiary amyl alcohol used.

9. Results

Yield obtained with different amine bases in tertiary amyl alcohol

Amine Base	% Yield
N,N-Diisopropylethylamine	80.00
Triethylamine	70.17
Tri-n-butylamine	38.85
Tri-isobutylamine	0.22
Tri-n-hexylamine	16.30
N,N-Dimethylcyclohexylamine	5.05

Yield obtained using N,N-Diisopropylethylamine in different tertiary alcohols

Tertiary Alcohol	% Yield
Tertiary amyl alcohol	80.00
Pinacol (2,3-dimethyl-2,3-butanediol)	81.02
3,7-Dimethyl-3-octanol	68.51

10. Conclusions

I believe that these results show that N,N-Diisopropylethylamine (Hünig's base) is a superior amine base in terms of the yield of 3-isochromanone obtained and that they also show that other tertiary alcohols are suitable for carrying out the invention process.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signed

Alan John Whitton
(Alan John WHITTON)

Dated this 7th day of December 2004